Klaus & Fanaroff

CARE OF THE HIGH-RISK NEONATE

Fifth Edition

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This book is dedicated to all students of perinatology, our patients and their parents, and to Phyllis, Susan, Alisa, and Sarah Klaus; David, Laura, Michael and Abigail Klaus; Laura, David, Emily, Sharon, and Benjamin Abada; Roslyn, Jonathan, and Amanda Fanaroff; Jodi, Peter, Austin, and Morgan Tucker.

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Antenatal and Intrapartum Care of the High-Risk Infant; The Physical Environment; Nutrition and Selected Disorders of the Gastrointestinal Tract: Part Two, Selected Disorders of the Gastrointestinal Tract and Part Three, Necrotizing Enterocolitis

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The Outcome of Neonatal Intensive Care

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Resuscitation of the Newborn Infant

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Care of the Parents

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Drug Dosing Table

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Drugs Used for Emergency and Cardiac Indications in Newborns; Drug Dosing Table; Umbilical Vessel Catheterization

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Brain Disorders of the Fetus and Neonate

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Drug Dosing Table

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PREFACE

Remarkably it has been 27 years since the first edition of *Care of the High-Risk Neonate* was published. Great strides have been taken in the care of high-risk infants, and the outcome for the most complex neonatal disorders is more favorable. Survival rates for even the most immature infants have improved enormously; however, the severe morbidity and long-term neurodevelopmental handicaps among this population remain a major concern. The foundations for the practice of evidence-based neonatology have been laid by a large number of multicenter, randomized trials. Meta-analyses and summation of these trials in the Cochrane Database and other contemporaneous publications assist the practitioners in formulating their care pathways and help ensure the best possible outcomes.

To incorporate the major advances that have occurred since the fourth edition as well as to view the field of neonatal-perinatal medicine in a critical fashion, all the chapters of this fifth edition have undergone significant revision. We are pleased to once again welcome several new contributors. One third of the chapters have been rewritten by new contributors who have diligently adhered to the basic format but presented a host of new ideas, fresh approaches, and differing views.

New information is presented in the form of text, critical comments, case problems, or simple questions. Overall, our objective has remained the same: to stimulate the readers and to provide a sound physiologic and experimental basis for perinatal care.

We have been most gratified to learn that this book continues to serve as a guide and companion for neonatal health care providers in many parts of the world. Our task of completing this fifth edition has been most pleasurable because of the expert editorial assistance provided by Bonnie Siner and Dolores Meloni at W.B. Saunders. We are deeply indebted to them as well as to the many contributors and commenters.

MARSHALL H. KLAUS
AVROY A. FANAROFF

Table of Contents

1

Antenatal and Intrapartum Care of the High-Risk Infant

Avroy A. Fanaroff
Robert Kiwi
Dinesh M. Shah

> Everything ought to be done to ensure that an infant be born at term, well developed, and in a healthy condition. But in spite of every care, infants are born prematurely.
>
> *Pierre Budin,* The Nursling

Parallel to the significant improvements in care of the premature and sick neonate, extensive technology concerned with the evaluation and supervision of the high-risk fetus has developed.[35, 150, 153, 180] Initially stimulated in the 1960s by the pioneering work with amniotic fluid analysis in Rh-isoimmunized pregnancy, this technology has evolved and expanded at a rapid rate. Hormonal assessments of fetoplacental function; fetal scalp blood determinations of fetal homeostasis, electronic monitoring of the fetal heart rate (FHR) during and before labor; biochemical estimations of fetal pulmonary maturity; ultrasonic measurements of fetal head size, fetal growth, and fetal activity; and detailed ultrasonic evaluation of fetal anatomy have all become commonplace procedures.[6, 8, 57]

The inner sanctum of the fetus has been penetrated and it has become commonplace to detect many genetic and antenatal abnormalities before delivery. Visualization of the fetus by fetoscopy and ultrasonic recording of fetal respiration, tone, and state, together with monitoring of fetal behavioral responses are an integral part of antepartum care. Detailed studies of fetal cardiac and renal anatomy and function present valuable information to the perinatal team.[52, 53] The capabilities of accurate diagnosis and treatment of fetal disorders have expanded rapidly so that fetal blood sampling, major surgical interventions such as repair of a diaphragmatic hernia, and excision of CCAM (congenital cystic adenomatoid malformation) or even correction of neural tube defects may be accomplished without interrupting the pregnancy.[55, 69, 71] Furthermore, intravascular transfusions for Rh isoimmune fetal anemia or other causes of reversible fetal anemia as well as medical treatment of fetal arrhythmias are possible.

EDITORIAL COMMENT: Minimally invasive fetal surgery appears to constitute a feasible approach to nonlethal fetal malformations that result in progressive and disabling organ damage. The concept that performing in utero surgery could protect the exposed but initially well-developed and uninjured spinal cord, prevent secondary neural injury, and preserve neural function in the human fetus with myelomeningocele has become a reality.

Meuli M, Meuli-Simmen C, Hutchins GM, et al: The spinal cord lesion in human fetuses with myelomeningocele: implications for fetal surgery. J Pediatr Surg 32:448–452, 1997.

Tulipan N, Hernanz-Schulman M, Bruner JP: Reduced hindbrain herniation after intrauterine myelomeningocele repair: A report of four cases. Pediatr Neurosurg 29:274–278, 1998.

These and other sophisticated approaches have rapidly become routine components of clinical care. However, many of these procedures are expensive and need quality laboratory support, and their results are not always easy to interpret. Advanced training and accreditation for obstetric perinatologists have followed the introduction of new technology, but in this, as in other allied areas, the supply of personnel remains limited. Furthermore, epidemiologic studies have indicated that only a small percentage of all pregnant women manifest risk features that necessitate these intensive interventions. Practicalities demand that they be applied in an appropriately effective fashion

because underutilized personnel and facilities will not be tolerated by a society increasingly concerned with maximizing cost-benefit ratios and reducing costs.

COMMENT: Nor should overutilization be tolerated. Although perinatal technologies and services are available, their use must be based on a reasonable amount of information about risks, benefits, and alternatives. Health care providers must be vigilant to avoid indiscriminate use of tests and facilities since they may result in more harm than benefits.

Denise Campbell

Nevertheless, in many centers of excellence, the appropriate utilization of the available technology appears to have contributed to marked reductions of perinatal mortality even among groups of very high-risk patients.[135, 191] It is hoped that wider and more uniform application of these newer concepts of care after controlled studies evaluating their benefits may, in part, offer a solution to the longstanding problem of unacceptably high perinatal mortality and morbidity in the United States. Overall, perinatal mortality rates have decreased dramatically, such that most centers are reporting a rate of 9 in 1000 live births in the surfactant era.[167, 191] Nonetheless, urgent need to tackle the problem of prematurity to reduce these rates further persists. The recent declines in mortality rates have been attributed to improved neonatal care, with no evidence to date of any impact on the prematurity rate. Neonataologists and perinatologists cannot claim all the credit for reductions in neonatal mortality. Changes in the birth weight and gestational age makeup of the newborn population accounted for 34% of the reduction in neonatal mortality rates in North Carolina from 1968 to 1977. Doing away with poverty would have an even greater effect in reducing the prematurity rate and the number of neonatal deaths.

Because many of the determinants of neonatal outcome relate directly to intrauterine and intrapartal events, continued improvement in perinatal care is contingent on a team approach to high-risk pregnancies. Obstetricians, midwives, nurses, pediatricians, and family physicians collaboratively must develop comprehensive protocols of management that will ensure the best results for the maximum number of mothers and infants.

Maximizing the benefits of the available technology requires regionalization—specifically, the development of a network of providers of perinatal care within a defined geographic area to implement the following objectives: (1) the identification of high-risk pregnancies early in the perinatal period, (2) the further identification of high-risk factors within the intrapartum period, (3) the development of interhospital agreements on criteria for transfer of mothers and infants within the network, (4) the development of support systems of consultation, laboratory services, education, and transportation within a region, and (5) the development of a record-keeping system that will allow adequate monitoring of the performance of the entire program.[100, 156]

EDITORIAL COMMENT: Paneth et al[139] noted that the mortality rate for full-term, appropriate size for gestational age infants in New York was not influenced by hospital of birth. However, the risk for death increased 24% if preterm infants were delivered at level I or II centers as compared with level III units. These small infants constituted only 12% of the births but accounted for 70% of the deaths. Extrapolation of these data to the rest of the United States makes a compelling case for delivery of preterm infants at tertiary centers.

Phibbs et al[145] examined the effects of neonatal intensive care unit (NICU) patient volume and the level of NICU care available at the hospital of birth on neonatal mortality for all nonfederal hospitals in California with maternity services. Hospitals were classified by the level of NICU care available (no NICU: level I; intermediate NICU: level II; expanded intermediate NICU: level II+: tertiary NICU: level III) and by the average patient census in the NICU. They observed that patient volume and level of NICU care at the hospital of birth both had significant effects on mortality. Compared with hospitals without an NICU, infants born in a hospital with a level III NICU with an average NICU census of at least 15 patients per day had the lowest risk-adjusted neonatal mortality rate. Furthermore, despite the differences in outcomes, costs for the birth of infants born at hospitals with large level III NICUs were not more than those for infants born at other hospitals with NICUs. The original principles of regionalization hold true despite efforts of managed care organizations to disrupt the process.

◆ IDENTIFYING THE PATIENT AT RISK

Early identification of the high-risk population associated with the largest proportion

of untoward perinatal outcomes has become a priority for the obstetric care delivery system. Many of the principal determinants of perinatal morbidity and mortality have been delineated. Included among these are maternal age, race, socioeconomic status, nutrition, past obstetric history, associated medical illness, and current pregnancy problems.

Careful analysis indicates that these determinants of morbidity and mortality are composed of historical factors existing before pregnancy as well as factors and events associated directly with pregnancy. Together these have provided the basis for the development of several assessment techniques capable of distinguishing most of the high-risk patients from the low-risk patients before delivery.

In 1969, Nesbitt and Aubry[133] indicated that 29% of pregnant women could objectively be identified as being at increased risk. The outcome of pregnancy among these women was judged unsatisfactory by the occurrence of premature birth, low-birthweight, perinatal mortality, neonatal depression, and respiratory distress syndrome at a rate twice that of the normal population. In Canada, similar results were obtained on more diverse groups of pregnant women by Goodwin et al.[60] Hobel et al[74] described a risk assessment system that included intrapartum as well as prenatal risk factors and identified four subgroups of patients with ascending rates of perinatal mortality and neonatal morbidity. In a prospective study of a low socioeconomic population, 18% of pregnant women were categorized as being at high risk both prenatally and intrapartally, and it was from this group that the poorest outcomes were obtained.

In many communities, perinatal teams use uniform record keeping and risk identification across broad populations of pregnant women. In this manner it is hoped to better define high-risk indicators among diverse socioeconomic groups.

Prematurity remains the most significant perinatal problem, accounting for 75% of all perinatal deaths. In the United States, the prematurity rate (~10%) has remained remarkably constant. In San Francisco, Creasy et al,[34] in an effort to identify and intervene in those cases in which patients are at greatest risk of delivering prematurely, developed an evaluation (scoring) system that takes into account (1) the patient's socioeconomic status, (2) her past history, (3) her daily habits, and (4) current pregnancy events. The patients were evaluated at their first office visit and again between 25 and 28 weeks' gestation. Those with a score of 10 were classified as being at high risk for preterm delivery (Table 1–1).

Of high-risk patients, 30% delivered prematurely, in contrast to only 2.5% among the low-risk group. In the second phase of the study, those identified as high risk were observed closely and instructed to report immediately any signs or symptoms compatible with early onset of labor. Furthermore, the perinatal staff received in-service education emphasizing (1) the need to respond promptly to any subtle signs of preterm labor, (2) the need to admit and observe closely with electronic monitoring those patients with mild signs of early preterm labor or cervical dilation, (3) the need to attempt tocolysis aggressively when premature labor was present, and (4) an awareness of the contraindications and side effects of tocolysis. Institution of these protocols resulted in a decrease in the prematurity rate from 6.75% to 2.4%. Bouyer et al,[17] using a program comprising (1) risk identification via a scoring system, (2) education of women at risk with emphasis on lifestyle and evaluation of uterine contraction and fetal movement, and (3) obligatory rest and a diminished workload for women identified at risk, were able to significantly reduce the prematurity rate in a region of France from 6% to 4% with a marked reduction in deliveries at less than 32 weeks' gestation.

Strategies to improve the outcome of premature babies have focused on antenatal prevention of conditions associated with low-birth-weight, together with intensive education, extensive intrapartum evaluation, and monitoring with sophisticated and aggressive care of the low-birth-weight fetus and infant. Simple measures in antenatal care such as elimination of cigarette smoking, improved nutrition, eradication of genitourinary tract infection, and increased awareness of the hazards of preterm birth have contributed to lower rates of prematurity.

EDITORIAL COMMENT: The goal of tocolytic therapy is to reduce neonatal morbidity and mortality by delaying delivery until 34 weeks of gestation, or at least for 48 hours, to allow time for the therapeutic effects of corticosteroids. Nitroglycerin, a nitric oxide donor, successfully

Table 1–1. Scoring System for Risk of Preterm Delivery

Points*	Socioeconomic Status	Past History	Daily Habits	Current Pregnancy
1	Two children at home Low socioeconomic status	One abortion <1 y since last birth	Works outside home	Unusual fatigue
2	<20 y >40 y Single parent	Two abortions	>10 cigarettes/d	<13 lb gain by 32 wk Albuminuria Hypertension Bacteriuria
3	Very low socioeconomic status <150 cm <45 kg	Three abortions	Heavy work Long, tiring trip	Breech at 32 wk Weight loss of 2 kg *Head engaged* Febrile illness
4	<18 y	Pyelonephritis		Metrorrhagia after 12 wk of gestation Effacement Dilation Uterine irritability
5		Uterine anomaly Second-trimester abortion Diethylstilbestrol exposure		Placenta previa Hydramnios
10		Premature delivery Repeated second trimester abortion		Twins Abdominal surgery

*Score is computed by addition of number of points given any item. 0–5 = low risk; 6–9 = medium risk; ≥10 = high risk.
Adapted from Creasy R, Gummer B, Liggins G: System for predicting spontaneous preterm birth. Obstet Gynecol 55:692, 1980. Reprinted with permission of the American College of Obstetricians and Gynecologists.

inhibits uterine contractions in sheep and monkeys and is one of the newer agents undergoing evaluation in humans.

These regionally successful programs have not easily been replicated when these principles were applied to a broader population base and consequently have not translated into a successful national strategy. In particular, the scoring systems as outlined herein have not been discriminating enough to identify patients at risk in order to implement an appropriate intervention program.

EDITORIAL COMMENT: The potential benefits and cost savings of reducing the number of premature deliveries assume astronomic proportions. Because there is no single "magic bullet," it is imperative to apply the knowledge gained from large controlled trials and the principles founded on the molecular mechanisms of human parturition. These include avoidance of multifetal pregnancies resulting from iatrogenic excesses of assisted reproduction and appropriate identification and treatment of sexually transmitted and genitourinary infections including bacterial vaginosis and group B streptococcal bacteriuria.[57] By applying such aggregate knowledge to women at risk for preterm birth MacGregor significantly reduced the rate of prematurity by half with estimated yearly savings of $2.5 million.[106]

The search for other indicators of premature labor or premature rupture of membranes continues with renewed vigor.

◆ EVALUATION OF FETUS AND SUPERVISION OF CARE

Improved physiologic understanding and multiple technologic advancements now provide the obstetrician with tools for objective evaluation of the fetus. In particular, specific information can be sought and obtained relative to fetal anatomy, growth, well-being, and functional maturity, and these data are used to provide a rational approach to clinical management of the high-risk infant before birth. For detailed reviews of the many new physical, hormonal, and biochemical approaches to prenatal and fetal assessments, refer to more comprehensive obstetric texts.[25, 35, 71] This section summarizes the clinical applications of the most widely used techniques as background for a discussion of practical clinical problems.

Monitoring Fetal Growth

It is important to emphasize that no test or laboratory procedure can supplant the data obtained from a careful history and physical examination. Ultimately, the results of all of the newer techniques have to be interpreted in light of the true or presumed gestational age of the fetus. It is, therefore, essential that the initial pregnancy visit be concerned with a thorough documentation of information relative to the regularity of the patient's menstrual cycles, use of oral contraceptive agents, date of last menstrual period, pregnancy test results, and the like. The initial and subsequent physical examinations are then approached with these facts in mind to ascertain whether the uterine size and growth are consistent with the supposed length of gestation. Similarly, the milestones of quickening (16 to 18 weeks) and fetal heart tone auscultation by Doppler ultrasound (12 to 14 weeks) and fetoscope (18 to 22 weeks) are important and need to be systematically recorded. Although most of this information is gathered early in pregnancy, it may not be used until later in gestation when decisions regarding the appropriateness of fetal size and the timing of delivery are contemplated.

Irregular menstrual cycles, use of oral contraceptives around the conception cycle (resulting in delayed ovulation), and discrepancies in either direction of size versus dates or expected gestational age indicate the need for an ultrasound evaluation to determine the fetal gestational age on the basis of biometric parameters. Ultrasound is a technique by which short pulses (2 μs) of high-frequency (approximately 2.5 MHz), low-intensity sound waves are transmitted from a piezoelectric crystal (transducer) through the maternal abdomen to the uterus and the fetus. The echo signals reflected back from tissue interfaces provide a two-dimensional picture of the uterine wall, placenta, amniotic fluid, and fetus. Diagnoses of multiple gestation, fetal structural abnormalities, abnormally implanted placentae, and uterine or placental pathologic conditions can be made by this technique. Serial measurements of the fetus can provide a reliable indicator of fetal growth. Furthermore, ultrasound is extensively used to assess fetal well-being and to study fetal physiology. Some indications for ultrasound are contained in Table 1–2. In many instances, ultrasound is performed to comply with the mother's request only.

Table 1–2. Uses of Ultrasound

Confirmation of pregnancy
Determination of
Gestational age
Fetal number and presentation
Placental location (vaginal bleeding)
Fetal anatomy (previous malformations)
Assessment of
Size/date discrepancy
Fetal well-being (biophysical profile—fetal tone, movements, and respiration)
Volume of amniotic fluid (suspected oligohydramnios or polyhydramnios)
Fetal arrhythmias
Fetal anatomy (abnormal alpha-fetoprotein)
Assist with procedures
Amniocentesis
Intrauterine transfusion

In the first trimester, the gestational age of the fetus is assessed by a crown-to-rump measurement. After the 13th week of gestation, measurement of the fetal biparietal diameter (BPD) or cephalometry is the most commonly used technique (Fig. 1–1). Before 20 weeks' gestation, this measurement provides a good estimation of gestational age within a range of plus or minus 10 days. After 20 weeks' gestation, the predictability of the measurement is less reliable, so an initial examination should be obtained before this state whenever possible. Such early examination also assists in interpretation of triple screen results as well in detection of major malformations. Follow-up examinations can then be done to ascertain whether fetal growth in utero is proceeding at a normal rate.

COMMENT: Low birth weight, defined as weight of less than 5 pounds, which results from either preterm delivery or intrauterine growth failure, is a universally recognized marker for poor perinatal outcome. The finding by Smith et al[163] that suboptimal growth during the first trimester predicts extreme premature birth and low birth weight at term gestation is not surprising.

Smith reported that, although significantly more infants who had subnormal first trimester growth were of low birth weight, the rate of perinatal death did not differ between those who were smaller than expected during the first trimester compared with those who were normal or larger than expected. Modern perinatal care has practically eliminated deaths of babies at term gestation except in cases of major con-

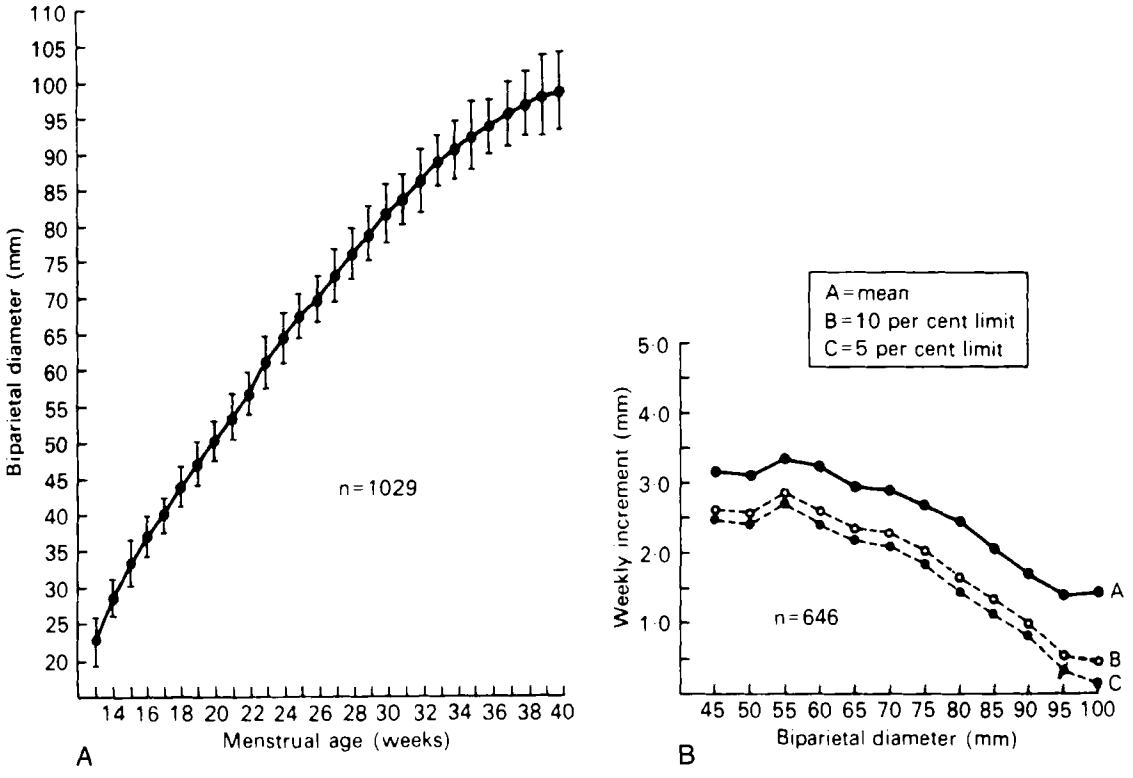

Figure 1–1. *A,* Mean fetal biparietal diameter (mm) ± 2 SD for each week of pregnancy from 13 weeks to term. *B,* Mean growth rate of fetal biparietal diameter with lower tolerance limits related to size of biparietal diameter. (From Campbell S: Fetal growth. In Beard R, Nathanielez P (eds): Fetal Physiology and Medicine: The Basis of Perinatology. Philadelphia: WB Saunders, 1976.)

genital malformations and rare cases of infection and asphyxia. Some maintain that the majority of term low-birth-weight children represent the normal distribution of growth rather than pathology.[27] On follow-up, these children have fairly good outcomes, with the exception of those born following asphyxia or with subnormal head growth and major congenital malformations.[86]

Maureen Hack

When fetal growth is retarded, however, brain sparing may result in an abnormal ratio of growth between the head and the rest of the body. Because the BPD may then remain within normal limits, other measurements are needed to detect the true retardation of growth. Campbell[20] has found that measurement of the ratio between the circumferences of head and abdomen is particularly valuable under these circumstances. During the second trimester of pregnancy, the normal ratio is greater than 1 in favor of the head, but after 36 weeks' gestation, there is a reversal and the abdominal circumference (AC) predominates. In many cases of growth retardation, this reversal is not seen (Fig. 1–2).

Femur length (FL), which may be less affected by alterations in growth than the head or abdomen, is used to aid in determining gestational age and to identify the fetus with abnormal growth. Serial assessment of growth and deviations from normal, including both macrosomia and growth retardation, helps to identify the fetus at risk during the perinatal period (see Chapter 4). Nonetheless, only approximately 50% of growth-retarded fetuses are identified before delivery. Calculation of estimated fetal weight (EFW) based on various fetal biometric parameters (BPD, head circumference [HC], AC, and FL) plotted against gestational age using various sonographic nomograms is an extremely useful method for serial assessment of fetal growth. Sophisticated computer software to serially plot EFW and provide percentile ranking of a given fetus are in common use at major perinatal centers.

EDITORIAL COMMENT: Guidetti et al[65] evaluated the efficacy of different methods of EFW

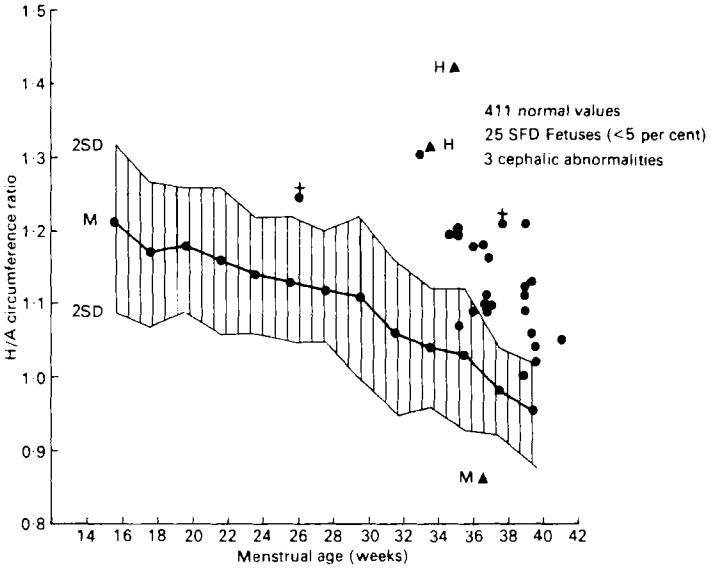

Figure 1–2. Head-to-abdomen (H/A) circumference ratio in small-for-dates (SFD) fetuses (i.e., below 5th percentile weight for gestation) and three fetuses with cephalic abnormalities; these are plotted on normal H/A ratio graph showing mean, 95th, and 5th percentile confidence limits. Of the 25 small-for-dates fetuses, 22 had ratios above 95th percentile limit, and two fetuses who died (+) had high ratios. Hydrocephalus *(H)* is associated with very high and microcephaly *(M)* with very low H/A ratios. (From Campbell S: Fetal growth. In Beard R, Nathanielez P (eds): Fetal Physiology and Medicine: The Basis of Perinatology. Philadelphia: WB Saunders, 1976.)

using sonographic measurements of the abdominal circumference, BPD, and FL, either alone or in combination in fetuses with suspected growth retardation. They reported that 75% of the EFWs using all three parameters, performed within 7 days of delivery, were within 110% of the actual birth weight. Estimates of fetal weight incorporating FL correlated best with actual birth weight.

In prospective studies using antenatal ultrasound,[6, 14, 157] no differences were noted in neonatal outcome from pregnancies in which ultrasound was not used. Nonetheless, early ultrasound has resulted in more confident establishment of dates, earlier detection of multiple gestation, and earlier diagnosis and more active intervention for infants with intrauterine growth retardation. Furthermore, no adverse, short-term effects from ultrasound have been noted. More women who had been screened with ultrasound required antenatal hospitalization.

A clear role for antenatal ultrasound has been established, and it is valuable in dating pregnancies, diagnosing multiple pregnancies, monitoring intrauterine growth, and detecting congenital malformation, (Fig. 1–3), as well as locating the placental site. Ultrasound is valuable when performing amniocentesis or attempting other invasive procedures such as intrauterine transfusions. Ultrasound may be used during labor to resolve problems related to vaginal bleeding, size or date discrepancies, suspected abnormal presentation, loss of fetal heart tones, delivery of a twin, attempted version of a breech presentation, and diagnosis of fetal anomalies.[157]

Assessing Fetal Condition Antepartum (Table 1–3)

The most widely used tests to evaluate the function and reserve of the fetoplacental unit and the well-being of the fetus before labor are stress and nonstress monitoring of the fetal heart rate (FHR), monitoring of fetal state and activity, and amnioscopy. Studies of fetal movements and respirations incorporated as part of the multivariable assessment (see discussion of fetal biophysical profile) continue to be used clinically.[99]

Antepartum Fetal Heart Rate Monitoring

Antepartum electronic monitoring of the FHR has provided a useful approach to fetal evaluation. The oxytocin challenge test described by Ray et al[148] records the responsiveness of the FHR to the stress of induced uterine contractions and thus attempts to assess the functional reserve of the placenta. A negative test (no FHR decelerations in response to adequate uterine contractions) gives reassurance that the fetus is not in immediate jeopardy.[189] Similar information may be obtained by evaluating the response of the FHR to spontaneous uterine contrac-

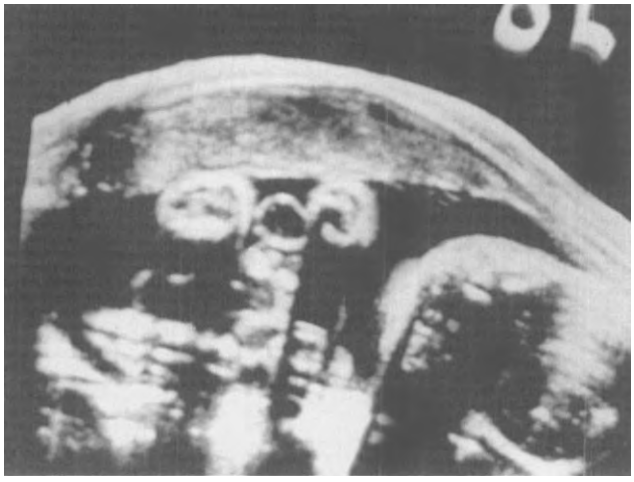

Figure 1–3. Gastroschisis with polyhydramnios.

tions and perhaps also from the resting heart rate patterns without contractions.[152, 158] Baseline variability of the FHR and accelerations of the rate with fetal motion have been reported as good indicators of the response to subsequent stress testing and of fetal well-being[152] (Table 1–4).

The contraction stress test evaluates uteroplacental function and was traditionally performed by initiating uterine contractions with oxytocin (Pitocin). Because continuous supervision and an electronic pump is required for regulated oxytocin infusion, and because of the invasiveness of intravenous infusion, attempts have been made to induce uterine contractions with nipple stimulation either by automanipulation or with warm compresses. Nipple stimulation has a variable success rate and, because of inability to regulate the contractions as well as concerns raised by the observation of uterine hyperstimulation accompanied by FHR decelerations, it has not gained wide acceptance. Nonetheless, breast stimulation provides an alternative, cheap technique for initiating uterine contractions and evaluating placental reserve.[89]

Table 1–3. Assessment of the Fetus

Throughout Pregnancy
Gestational age: history, uterine growth, quickening, first heart sounds, ultrasound
Fetal growth
Serology, maternal antibodies
Amniotic fluid volume
Ultrasound: fetal number, growth, anomalies, fetal well-being
Risk assessment
First and Second Trimesters
Alpha-fetoprotein
Chorionic villus sampling
Amniocentesis
Cordocentesis
Third Trimester
Nonstress, stress tests
Formal fetal movement counting
Fetal biophysical profile
Amniotic fluid phospholipids and bilirubin
Perinatal Period
Continuous fetal heart rate monitoring
Fetal scalp pH
Cord blood gases

An antepartum demise of 1 to 4 in 1000 may be anticipated despite a reactive nonstress test (NST). The frequency of doing an NST is also important. In certain high-risk pregnancies in which the fetal status may change in less than a week (e.g., insulin-dependent diabetes mellitus in pregnancy), an NST performed twice a week at equidistant intervals results in lower perinatal mortality rate (less than 1 in 1000). On the other hand, in up to 90% of patients, a nonreactive NST indicates a fetal sleep state and is not associated with fetal jeopardy.[172] Vibroacoustic stimulation, using devices emitting sound levels of approximately 80 dB at a frequency of 80 Hz, results in FHR acceleration and reduces the rate of falsely worrisome NSTs. Thus, the specificity of the NST may be improved by adding sound stimulation.

The modified NST comprises vibroacoustic stimulation, initiated if no acceleration is noted within 5 minutes during the standard NST. Because reactivity is defined by two

Table 1–4. Criteria for Interpreting Nonstress Test (NST) and Acoustic Stimulation Test (AST)

Reactivity Terms	Criteria
Reactive NST	Two fetal heart rate (FHR) accelerations of at least 15 bpm, lasting a total of 15 s, in 10-min period
Nonreactive NST	No 10-min window containing two acceptable (as defined by reactive NST) accelerations for maximum of 40 min
Reactive AST	Two FHR accelerations of at least 15 bpm, lasting a total of 15 s, within 5 min after application of acoustic stimulus or one acceleration of at least 15 bpm above baseline lasting 120 s.
Nonreactive AST	After three applications of acoustic stimulation at 5-min intervals, no acceptable accelerations (as defined by reactive AST) for 5-min after third stimulus

accelerations within 10 minutes, the sound is repeated if 9 minutes have elapsed since the first acceleration.

EDITORIAL COMMENT: While the effectiveness of *vibroacoustic stimulation* in assessing the health of the fetus continues to be studied, its safety for the fetus has come under scrutiny. Detailed evaluation of 10 healthy women with normal pregnancies of 37 to 40 weeks' gestation noted that stimulation with an electronic artificial larynx (EAL) *induced excessive fetal movements sometimes lasting as long as an hour, a prolonged tachycardia, nonphysiologic state changes, and a disorganization and change in the distribution of fetal behavioral states.*[182] Using simultaneous ultrasound during stimulation, Smith et al surprisingly *noted that 20 of 21 fetuses urinated at its onset.* Although during labor 47% of fetuses do not respond to EAL despite normal blood gases, during antenatal testing the absence of a response could simply mean the fetus is sleeping. Is this device harmful when it causes most fetuses to urinate and some fetuses to move for longer than an hour?

Clark[28] reported that, when using the modified NST, the testing time averaged 10 minutes, 2% of the tests were nonreactive, intervention was indicated in 3%, and mortality rate was low (0.01%).

Quicker and as effective as the contraction stress test or the biophysical profile, the modified NST has become the testing scheme of choice.

Monitoring Fetal Activity

Fetal movement has gained increased attention as an expression of fetal well-being in utero. It has been monitored simply by maternal recording of perceived activity or using pressure-sensitive electromechanical devices and real-time ultrasound. Fetal inactivity is generally defined as less than three movements per hour. Whereas evidence of an active or vigorous fetus is reassuring, an inactive fetus is not necessarily an ominous finding and may merely reflect fetal state (fetal activity is reduced during quiet sleep, by certain drugs including alcohol and barbiturates, and by cigarette smoking). Nonetheless, fetal inactivity requires prompt reassessment including real-time ultrasound or electronic FHR monitoring.

Formal Fetal Movement Counting[61, 123]

With a goal of decreasing the stillbirth rate near term, there has been an increased tendency to use fetal movements as an indicator of fetal well-being. The test is simple and can be administered frequently by a compliant and perceptive mother, preferably every night when the fetus is more active. The mother documents how long it takes to feel 10 kicks and maintains accurate "kick sheets" for review by the medical staff. Fifty percent of women feel 10 kicks in less than 20 minutes, and if the woman does not feel 10 kicks in 2 hours, she is instructed to come to the hospital for an NST. The use of kick counts has been associated with a 50% increase in the number of NSTs and an increased rate of obstetric intervention for fetal compromise. Moore and Piacquadio,[123] with the aid of historical control subjects, noted that the test reduced fetal mortality rate, but a larger prospective controlled trial from Europe failed to demonstrate that routine formal fetal movement counting

achieved such an effect. The test is certainly worth instituting for selected high-risk patients as they approach term. It has the advantages of being inexpensive and of providing continual reassurance to anxious mothers between fetal evaluation visits, especially in high-risk conditions wherein the fetal status may change in a short time (e.g., insulin-dependent diabetes mellitus [IDDM]).

Fetal Biophysical Profile

Antepartum stillbirths account for 66% of all perinatal deaths and are the result predominantly of chronic asphyxia and congenital malformations. There is an urgent need to detect developing fetal asphyxia accurately in order to intervene and reduce fetal wastage appropriately. A composite of fetal functions, the biophysical profile, has emerged to address this issue.

EDITORIAL COMMENT: Fretts and associates[48] reported on the changing patterns of fetal death over 3 decades. The fetal death rate (per 1000 births) diminished from 11.5 in the 1960s to 5.1 in the 1980s. Significant changes over this time period include virtual elimination of fetal deaths caused by intrapartum asphyxia and Rh isoimmunization and significant decreases in unexplained fetal deaths and those caused by fetal growth retardation. The continued toll is due to intrauterine infections, lethal malformations, growth retardation, and abruptio placentae, which remains the largest identifiable cause of fetal death.

Six variables—the NST, fetal movements, fetal breathing movements, fetal tone, amniotic fluid volume, and placental grading—constitute the fetal biophysical profile (Table 1–5). A modified biophysical profile refers to sonographic components of the composite test (i.e., excludes NST) and is commonly used as a follow-up test for a nonreactive NST. There has been much debate regarding the pros and cons of each component of this evaluation. However, in a prospective evaluation, normal tests were highly predictive of a good neonatal outcome. In contrast, each abnormal variable was associated with a high false-positive rate. Vintzileos et al[181] noted that the absence of fetal movements was the best predictor of abnormal FHR patterns in labor (80%), the nonreactive NST best predicted meconium-stained amniotic fluid (33%), and decreased tone was the best predictor of perinatal death. The biophysical profile was far superior to the contraction stress test in predicting the hypoxic fetus (71% versus 16%). Because

Table 1–5. Technique of Biophysical Profile Scoring

Biophysical Variable	Normal (score = 2)	Abnormal (score = 0)
Fetal breathing movements	At least 1 episode of at least 30-s duration in 30-min observation	Absent or no episode of ≥30 s in 30 min
Gross body movement	At least three discrete body/limb movements in 30 min (episodes of active continuous movement considered as single movement)	Two or fewer episodes of body/limb movements in 30 min
Fetal tone	At least one episode of active extension with return to flexion of fetal limb(s) or trunk; opening and closing of hand considered normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absent fetal movement
Reactive fetal heart rate	At least two episodes of acceleration of ≥15 bpm and a least 15-s duration associated with fetal movement in 30 min	Less than two accelerations or accelerations <15 bpm in 30 min
Qualitative amniotic fluid volume	At least one pocket of amniotic fluid that measures at least 1 cm in two perpendicular planes	Either no amniotic fluid pockets or a pocket <1 cm in two perpendicular planes

From Manning F, Morrison I, Lange I, et al: Antepartum determination of fetal health: Composite biophysical profile scoring. Clin Perinatol 9:285, 1982.

the biophysical profile incorporates ultrasonic evaluation of the fetus and may result in the detection of anatomic abnormalities, some investigators have proposed that it should be used as the primary method of fetal surveillance.

Experience with composite biophysical profile scoring has been encouraging, with a reduction in perinatal mortality rate and increased detection of fetal anomalies. A high sensitivity (few fetal asphyxial deaths) and high specificity (minimal inappropriate intervention) are noted from these reports. This contrasts sharply with the high incidence of false-positive tests observed with single assessments such as fetal movements or fetal breathing. A normal fetal biophysical profile appears to indicate intact central nervous system (CNS) mechanisms, whereas factors depressing the fetal CNS reduce or abolish fetal activities. Thus, hypoxemia decreases fetal breathing and, with acidemia, reduces body movements. CNS stimulants increase fetal activities. The biophysical profile offers a broader approach to fetal well-being. Perinatologists have become attuned to doing multiple tests in evaluating fetal well-being, resulting in wider acceptance of the biophysical profile.

Alpha-Fetoprotein

Alpha-fetoprotein (AFP) is a fetal serum protein genetically and biochemically related to albumin. It has become a valuable marker not only in the prenatal detection of open neural tube defects but also in identifying fetuses likely to have chromosomal abnormalities.[116]

Maternal serum AFP measurement has proven to be the most effective prenatal screening program yet devised. The fetal liver is the primary site of synthesis of AFP and by 15 to 20 weeks of pregnancy, AFP is a major component of fetal serum. The AFP in amniotic fluid at 15 to 20 weeks is mainly derived from fetal urination with a small contribution through the fetal skin. Any pregnancy complication or birth defect that causes fetal serum to leak or exude into the amniotic fluid elevates amniotic fluid AFP and subsequently maternal serum AFP levels. Examples include anencephaly, open spina bifida, epidermolysis bullosa, gastroschisis, omphalocele, and amniotic bands. Furthermore, abnormalities in the volume of amniotic fluid may be reflected by abnormal AFP values. Additionally, a fetomaternal bleed may also result in elevated maternal AFP levels without increasing amniotic fluid levels.

Studies in the United Kingdom documented the correlation of an elevated amniotic fluid AFP level between 16 and 18 weeks' gestation with open neural tube defects. Subsequent testing demonstrated elevated maternal serum AFP levels as well for those fetuses with open defects, and this knowledge has been translated into worldwide screening programs that use maternal serum. These programs have been very successful, particularly when it is noted that neural tube defects predominantly occur (95%) in families with no prior history of such defects. The analysis of amniotic fluid has proved to be a reliable, accurate diagnostic test for open neural tube defects, with a 98% to 99% correlation between amniotic fluid AFP values (plus 3 or more standard deviations from the mean) and affected fetuses.

In addition to open neural tube defects, fetal demise and other fetal anomalies also have an elevated amniotic fluid AFP level; these include abdominal wall defects (gastroschisis and omphalocele), upper gastrointestinal obstruction, congenital nephrosis, and Turner syndrome.

A new correlation between low maternal serum AFP levels and fetal anomaly has also been recognized. First reported by Merkatz et al,[116] this phenomenon has been confirmed in a number of studies. Pregnancies involving fetuses with chromosomal aneuploidy, particularly trisomy 21 but also trisomy 18, have serum and amniotic fluid AFP levels significantly below the normal median. Application of this method can be of great value in identifying pregnancies at risk, particularly for mothers younger than 35 years of age.

Human chorionic gonadotropin (hCG) is elevated in women carrying aneuploid fetuses, unconjugated estriol is lower in women carrying fetuses with trisomy 21, and maternal serum AFP may be reduced with chromosomal abnormalities. The triple screen in which determinations of AFP are considered in conjunction with hCG and estriol have improved the reliability with which spina bifida and trisomy 21 are identified.[118, 127, 184, 185]

Although it will probably never be possible to eradicate neural tube defects, progress

has been made in diminishing their incidence, identifying and characterizing the defects, counseling families who choose to continue a pregnancy, and decreasing morbidity by optimizing management at the time of delivery. Incidentally, the prevalence of neural tube defects is naturally declining in the United States in all regions as monitored by the Centers for Disease Control and Prevention. The triumph for perinatal medicine has all been the result of beautifully integrated epidemiologic studies, prospective screening trials, rapid improvement in ultrasound imaging, implementation of rapidly evolving techniques of prenatal diagnosis, and better preoperative and postoperative care of mother and baby.

Trisomy 21 Screening

Screening of maternal serum to identify fetuses with Down syndrome is routinely offered during the second trimester of pregnancy. Prenatal screening by means of serum assays or ultrasonographic measurements, either alone or in combination, may also be possible in the first trimester. Neilson[131] notes that trisomic fetuses with pronounced nuchal translucency are more likely to die in utero.

Maternal age and abnormalities of serum pregnancy-associated plasma protein A and free β-hCG detects about 60% of affected fetuses by 10 to 14 weeks' gestation. The combination of maternal age and quadruple screening test, including Inhibin A, alpha-fetoprotein, hCG, and unconjugated estriol, can detect approximately 75% of affected fetuses by 15 to 22 weeks' gestation. Haddow's series included a total of 48 pregnancies affected by Down syndrome and 3169 unaffected pregnancies studied before 14 weeks of gestation. The rates of detection of Down syndrome for the five serum markers were as follows: 17% for alpha-fetoprotein, 4% for unconjugated estriol, 29% for hCG, 25% for the free beta subunit of hCG, and 42% for pregnancy-associated protein A, with false-positive rates of 5%. They concluded that screening for Down syndrome in the first trimester is feasible, with use of measurements of pregnancy-associated protein A and either hCG or its free beta subunit in maternal serum. Nuchal translucency is increased at 10 to 13 weeks in trisomy 21 fetuses, but its role alone or in combination with the aforementioned serum markers is still being evaluated. The skin edema in fetal trisomies is characterized by specific alterations of the extracellular matrix attributable to altered gene dosage.[183]

The accuracy of nuchal translucency measurement varies between examiners and between patients, likely in relation to examiner skill and image resolution. The size of translucency varies slightly with gestational age and crown-rump length and is independent of maternal age. Most authors have used a nuchal thickness of at least 2.5 mm or 3 mm to define abnormal, although some have suggested that the normal variation with gestation requires that different thresholds be used at different gestational ages. The presence of a thickened nuchal translucency is associated with chromosomal abnormality and perhaps with structural abnormality even when the karyotype is normal. D'Ottavio[41] found that increased nuchal translucency thickness (≥4 mm) at the 13- to 15-week scan was the most effective marker for chromosomal defects.

Because of the reported variations in the populations studied, the methods used, and the results of screening, it is inappropriate at this time to assign a numeric risk to any individual patient with this finding. Pandya,[138] in what was considered to be a "nonrepresentative population,"[151] reported that at 10 to 14 weeks' gestation the sensitivity of fetal neck translucency was 77% and the specificity 95%.[138] Haddow noted that measurements of nuchal translucency varied considerably between centers and could not be reliably incorporated into their calculations. Pajkrt[137] examined the effectiveness of nuchal translucency measurement in the detection of trisomy 21 in a low-risk population. A nuchal translucency of 3 mm or more identified 67% of the fetuses with trisomy 21, for an invasive testing rate of 2.2%. Screening by maternal age would have diagnosed six of nine fetuses (67%) with trisomy 21 for an invasive testing rate of 24%. After doing various risk assessments, the researchers concluded that nuchal translucency measurement is an effective screening method for trisomy 21 in an unselected obstetric population. In Greece, Theodoropoulos[173] reported that the combination of fetal nuchal translucency and maternal age were an effective means of screening for chromosomal abnormalities. An adjusted risk of 1 in 300 or more identified 10 of 11

fetuses with trisomy 21 and all 11 fetuses with other chromosomal defects.

Prenatal diagnosis of trisomy 21 currently relies on assessment of risk followed by invasive testing in the 5% of pregnancies at the highest estimated risk. Factoring in maternal age and combining first trimester ultrasonography with early serum screening may ultimately prove to be the most efficient means of screening for chromosomal anomaly, but although Snijders'[164] series included these criteria and detected almost 80% of affected pregnancies, it still required about 30 invasive tests to confirm the identification of one affected fetus.

EDITORIAL COMMENT: Prenatal screening for trisomy 21 incorporates estimation of risk on the basis of maternal age, serum concentration of various analytes, and ultrasound measurements. Because only 20% of infants with trisomy 21 are born to women 35 years or older, maternal age by itself has too low a sensitivity. During the first trimester, screening for Down syndrome uses ultrasound measurement of nuchal translucency (at 10 to 14 weeks' gestation) and measurements of the free beta subunit of hCG. This increases the sensitivity of first trimester screening to 80%. Second trimester screening has been improved by the addition of serum inhibin measurements to the triple screen, which included maternal serum alpha-fetoprotein concentration (low), serum hCG (elevated), and unconjugated estriol (low). Wald et al[187] proposed a new screening algorithm in which measurements obtained during both trimesters are integrated to provide a single estimate of a woman's risk of having a pregnancy affected by Down syndrome. They used data from published studies of various screening methods employed during the first and second trimesters. When they used a risk of 1 in 120 or greater as the cutoff to define a positive result on the integrated screening test, the rate of detection of Down syndrome was 85%, with a false-positive rate of 0.9%. To achieve the same rate of detection, current screening tests would have higher false-positive rates (5% to 22%) (Fig. 1–4). If the integrated test were to replace the triple test (measurements of serum alpha-fetoprotein, unconjugated estriol, and hCG), currently used with a 5% false-positive rate, for screening during the second trimester, the detection rate would be higher (85% vs. 69%), with a reduction of four fifths in the number of invasive diagnostic procedures and consequent losses of normal fetuses. Although the integrated test detects more cases of Down syndrome with a much lower false-positive rate than the best currently available test, it may not gain wide acceptance because patients detected as high risk in the first trimester are more likely to choose chorionic villus sampling (CVS) than wait for the repeat screening during the second trimester.

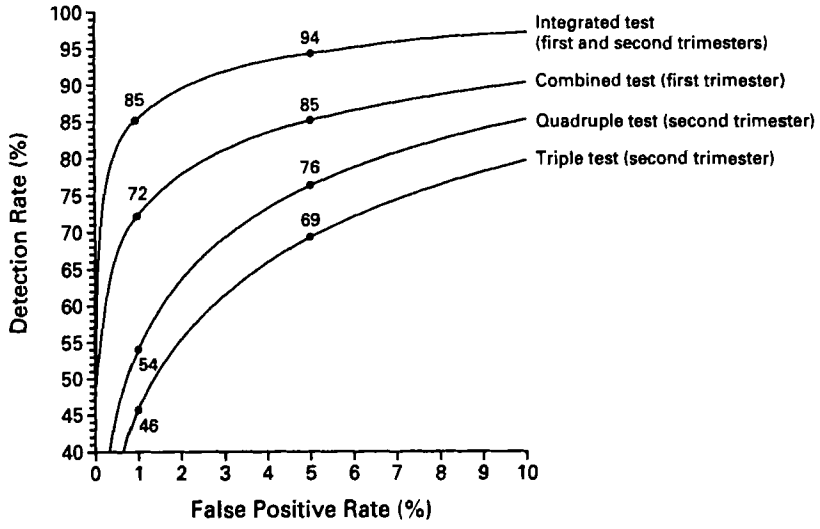

Figure 1–4. Rates of detection of Down syndrome and false positive rates for various screening tests. The triple test includes measurements of serum alpha-fetoprotein, unconjugated estriol, and human chorionic gonadotropin in the second trimester. The quadruple test includes measurements of serum alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin A in the second trimester. The combined test includes measurements of serum pregnancy-associated plasma protein A, free beta subunit of human chorionic gonadotropin, and nuchal translucency in the first trimester. The integrated test includes measurements of serum pregnancy-associated plasma protein A and nuchal translucency in the first trimester and measurements of serum alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin A in the second trimester.

Chorionic Villus Sampling[76, 150]

CVS is a method of prenatal diagnosis of genetic abnormalities that can be used during the first trimester of pregnancy. The major indications for chorionic villus sampling are to detect disorders related to maternal age and those that are sex linked, and to detect single gene disorders and hemoglobinopathies. Rhoads[150] reported that successful cytogenetic diagnoses were accomplished from 98% of 2235 attempts at CVS and from 99.4% of 651 amniocenteses. The total loss of desired pregnancies was 7% in the CVS group and 6% in the amniocentesis group. Thus, CVS permits early and accurate diagnosis but is not without hazard and should be used selectively.[150]

Although a screening test to identify a "high-risk" population would greatly improve the ability to diagnose congenital and acquired disease, the formulation of a noninvasive prenatal test that would provide all the diagnostic information currently available by amniocentesis and CVS without the risk of an invasive procedure remains a sentinel risk.

EDITORIAL COMMENT: A randomized trial (Medical Research Council) involving 3248 patients from 31 centers demonstrated that the policy of CVS in the first trimester reduced the chances of a successful pregnancy outcome by 4.6% (95% confidence intervals [CI] 1.6–7.5) when compared with second trimester amniocentesis. This was attributed to an increase in both spontaneous fetal deaths before 20 weeks and terminations of pregnancy for chromosomal anomalies. The observation of severe limb abnormalities following early (8 to 9 weeks) CVS raises further concerns.[76] The ideal time for performing CVS is between 10 and 12 weeks' gestation. Also, the consensus opinion, borne out by meta-analysis of the available data, is that CVS does not increase the risk for limb abnormalities. In the quest for earlier diagnosis, embryoscopy, a new invasive technique for direct visualization of the first trimester conceptus, has been used before elective termination. Incredibly clear pictures of the developing embryo are obtained, but it remains to be proven that the technique is safe and superior to transvaginal ultrasonography.

Assessing Fetal Maturity

The introduction of amniocentesis for study of amniotic fluid and Rh-immunized women paved the way for development of the battery of tests currently available to assess fetal maturity. The initial methods developed were based on amniotic fluid levels of creatinine, bilirubin, and fetal fat cells, and these provided a good correlation with fetal size and gestational age. They were, however, inadequate predictors of fetal pulmonary maturity.[115]

Amniocentesis to assess fetal pulmonary maturity is the currently accepted technique. Lecithin and sphingomyelin are present in amniotic fluid, and their relative ratios can be used for assessment of pulmonary maturity.[54] The risk of respiratory distress syndrome (RDS) is least when the ratio of lecithin to sphingomyelin (L:S) is greater than 2. However, this does not preclude the development of RDS in certain circumstances (i.e., IDDM or erythroblastosis). The presence of phosphatidylglycerol is a good indication of lessened risk of RDS with fewer false-negative results.

Because RDS is a frequent consequence of premature birth and a major component of neonatal morbidity and mortality in many high-risk situations, it was critical that an antenatal assessment of pulmonary status be developed. After it was found that the pulmonary surface-active materials needed for lung stabilization could be detected in the amniotic fluid and that their concentrations increased with gestational age, it followed that amniotic fluid analysis might yield insight into pulmonary maturation. Gluck and Kulovich[54] first measured the amniotic fluid L:S ratio in the third trimester of pregnancy and demonstrated its clinical application for the prediction of RDS (Fig. 1–5).

EDITORIAL COMMENT: RDS is the most common complication in preterm infants and is a significant, but diminishing, cause of death and severe morbidity. Thirty years of research has documented the beneficial effect of antenatal corticosteroids on fetal lung maturation. As a result, antenatal corticosteroids in combination with postnatal surfactant remains the mainstay of prevention and therapy for RDS in preterm infants. In 1994, a National Institutes of Health (NIH) consensus panel, on the basis of available evidence, recommended the use of corticosteroid therapy for delivery anticipated before 34 weeks of gestation when the fetal membranes are intact and before 32 weeks of gestation when the membranes are ruptured.[130] The beneficial effects of corticosteroid administration appear to be the greatest if more than 24 hours and less than 7 days have elapsed between

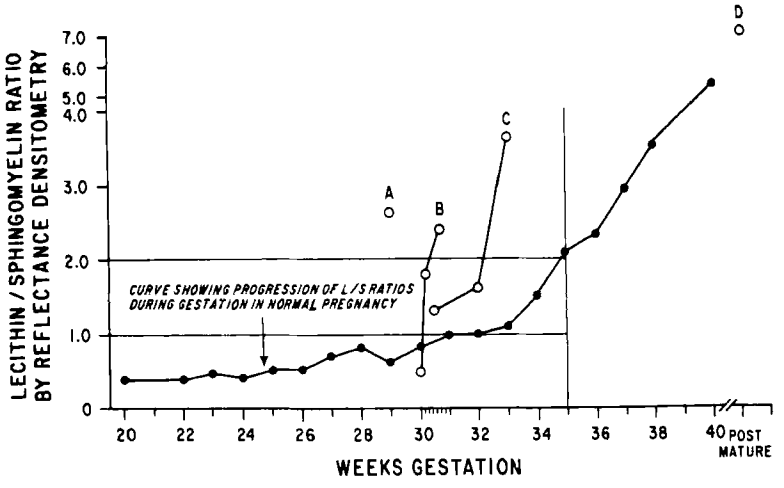

Figure 1–5. Abnormal elevations of lecithin/sphingomyelin (L:S) ratio as compared with curve of progress of L:S ratio of normal pregnancy. A = Chronic stress, retroplacental bleeding; B = acute stress, membranes ruptured 72 to 96 hours; C = acute stress, placental infarction; and D = chronic stress, postmaturity. (From Gluck L, Kulovich M: Lecithin-sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancy. Am J Obstet Gynecol 115:539, 1973.)

initial administration of therapy and actual delivery. However, even partial courses appear to have been beneficial. At the time of the consensus conference, corticosteroids were used in less than 20% of eligible patients, but since the conference, that number has increased to nearly 80%. Antenatal corticosteroids have decreased the incidence and severity of respiratory distress, lowered the mortality rate, and significantly reduced the incidence of major intraventricular hemorrhage. Antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of cystic periventricular leukomalacia among very premature infants.[10] An important secondary benefit of corticosteroid administration is the reduction in the cost and duration of neonatal hospitalization. The optimal number of courses of antenatal corticosteroids for lung maturation remains unclear. On the basis of a retrospective analysis of multiple courses of antenatal corticosteroids, Banks[8] reported that they did not improve outcome and were associated with increased mortality rate, decreased fetal growth, and prolonged adrenal suppression.

Because thyrotropin-releasing hormone (TRH) also accelerated pulmonary maturation, and there are still many infants with chronic lung disease, TRH was added to antenatal corticosteroids. A number of large multicenter trials universally reported that the combination regimen did not reduce the frequency of RDS or improve the outcome of preterm neonates compared with the use of corticosteroids alone.[7, 31, 37]

There are several advocates of the direct quantitative measurement of lecithin rather than the more qualitative L:S ratio. The introduction of the foam stability test by Clements and coworkers[29] provided a rapid, simple, inexpensive test for surfactant. As with the L:S ratio itself, this test provides two limits of reliable prognostic usefulness and an intermediate zone with more equivocal results. False-positive and false-negative results have been reported with both methods.[174] Investigators have noted that confirmation of the presence of phosphatidyl glycerol, a component of the more mature surfactant complex, reduces the incidence of false-positive tests. Nonetheless, in uncomplicated, unstressed situations such as elective repeat cesarean section, any of these techniques are useful, and their use should be encouraged, taking into consideration the risk of amniocentesis.

Phosphatidylglycerol can be measured by rapid tests and is not influenced by blood or vaginal secretion, and is therefore a good indication (in the presence of a positive test) of pulmonary maturity when sampled from a vaginal pool of fluid. Other tests have been used to reduce testing time and to increase the ease of interpretation. These include the foam stability (shake) test[29], the Lamadex-FSI test[159], and the amniotic fluid absorbance test at 650 nm.[176] Lamellar body counts—size similar to platelets—is a standard hematology counter that can be used; values of 30,000 to 50,000/μL indicate maturity.[4] The use of amniotic fluid testing for elective delivery at term has been replaced by accurate dating using ultrasound,[1] either crown-rump length at 6 to 11 weeks and an ultrasound at 12 to 20 weeks combined with additional evidence of gestational length at 30 weeks fetal heart tones (FHT) by Doppler or 36 weeks since a positive pregnancy test.[1] If any of these confirm a gestational age of 39 weeks, amniocentesis can be waived for delivery.